TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: SYL 531

U S APPLICATION NO. (If known, see 37 CFR 1.5): 09/937045

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR00/00697	21 March 2000	30 March 1999

TITLE OF INVENTION: DERIVATIVES OF 1,4-DIAZABICYCLO[3.2.2]NONANE-4-CARBOXYLATES AND -CARBOXAMIDES, THEIR PREPARATION AND THEIR THERAPEUTIC APPLICATION

APPLICANT(S) FOR DO/EO/US

Thierry Gallet, Samir Jegham, Patrick Lardenois, Alistair Lochead and Alain Nedelec

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1)).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application.
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An executed oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.

    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information:
    Citation of References
    Information Disclosure Statement by Applicant (Form PTO-1449)

JC16 Rec'd PCT/PTO SEP 2 0 2001

U.S. APPLICATION NO (if known, see 37 CFR 1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/937045	PCT/FR00/00697	SYL 531

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1. 492 (a)(1)-(5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and international Search Report not prepared by the EPO or JPO $1000.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $860.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO .. $710.00

International preliminary examination fee (37 CFR 1.482)paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4).................. $690.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfy provisions of PCT Article 33(1)-(4) $100.000

				CALCULATIONS	PTO USE ONLY
ENTER APPROPRIATE BASIC FEE AMOUNT =				$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	5 -20 =	0	x $18.00	$	
Independent claims	1 - 3 =	0	x $80.00	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $270.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 860.00	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$ 860.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$	
TOTAL NATIONAL FEE =				$ 860.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 860.00	
				Amount to be refunded:	$
				Charged	**$860.00**

a. ☐ A check in the amount of $__________________ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 19-0091 in the amount of **$860.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0091. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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27546
PATENT TRADEMARK OFFICE

[signature] 9/20/2001
SIGNATURE DATE

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE 09/937045

Filing under 35 U.S.C. § 371
Corresponding to International
Application No.: PCT/FR00/00697

Applicants: Thierry Gallet, Samir Jegham, Patrick Lardenois, Alistair Lochead and Alain Nedelec

International Filing Date: 21 March 2000

For: DERIVATIVES OF 1,4-DIAZABICYCLO[3.2.2]NONANE-4-CARBOXYLATES AND –CARBOXAMIDES, THEIR PREPARATION AND THEIR THERAPEUTIC APPLICATION

CERTIFICATE UNDER 37 C.F.R. 1.10

Express Mail Label Number: EL676470751US

Date of Deposit: September 20, 2001

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service on the date indicated above and is addressed to: Commissioner for Patents, Box PCT, Attn: EO/US, Washington, DC 20231.

Signature

Commissioner for Patents
Box PCT
Attn: EO/US
Washington, D.C. 20231

Dear Sir:

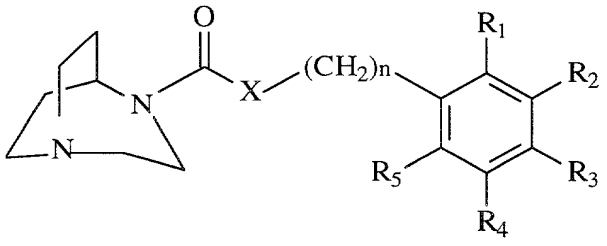
PRELIMINARY AMENDMENT

Please amend the above-identified application as follows:

In the Claims:

Please amend claims 1 and 3, cancel claim 2, and add new claims 4-6 as follows before calculating the filing fee for the above-identified application.

1. (amended) A compound corresponding to the general formula (I)



(I)

in which

X represents an oxygen atom or a group of formula NZ in which Z represents a hydrogen atom or a (C_1-C_6)alkyl group,

n represents a number 0, 1 or 2, and

R_1, R_2, R_3, R_4 and R_5 each represent, independently of each other, a hydrogen or halogen atom or a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenoxy or phenyl group optionally substituted with a halogen atom or a trifluoromethyl, cyano, hydroxyl, (C_1-C_6)alkyl or (C_1-C_6)alkoxy group, or alternatively R_2 and R_3 together form a group of formula $-OCH_2O-$ or $-CH_2CH_2CH_2CH_2-$, in the form of a base or of an addition salt with an acid.

3. (amended) A pharmaceutical composition comprising a compound according to Claim 1, combined with an excipient.

Please cancel claim 2.

Please add the following new claims:

4. (added) A compound according to claim 1 wherein X is O, NH or $NHCH_3$; n is 0 or 1; R_1 is hydrogen, bromo, methyl or methoxy; R_2 is hydrogen, methyl, methoxy, trifluoromethyl, fluoro or chloro; R_3 is chloro, bromo, methyl, methoxy, nitro, fluoro, hydrogen, phenyl, trifluoromethoxy or phenoxy; or R_2 and R_3 together form a group of the formula $-OCH_2O-$ or $-CH_2CH_2CH_2CH_2-$; R_4 is hydrogen; and R_5 is hydrogen or methoxy; in the form of a base or of an addition salt with an acid.

5. (added) A method for the treatment or prevention of disorders linked to nicotinic receptor dysfunction which comprises administering to a patient in need of such treatment an effective amount of a compound according to claim 1.

6. (added) A method for the treatment or prevention of disorders linked to nicotinic receptor dysfunction which comprises administering to a patient in need of such treatment an effective amount of a compound according to claim 4.

REMARKS

Claims 1 and 3 have been amended in order to write these claims in the appropriate U.S. claim format.

Claim 2 has been canceled.

Claims 4-6 have been added by the foregoing amendments. Support for claim 4 occurs, for example, at page 9 of the specification. Support for claims 5-6 occurs, for example, at page 12, lines 1-3 of the specification.

Claims1 and 3-6 remain in the application.

Attached hereto is a marked-up version of the changes made to the claims by the instant amendment. The marked-up version is entitled "Version With Markings To Show Changes Made".

Respectfully submitted,

Date: September 29, 2004

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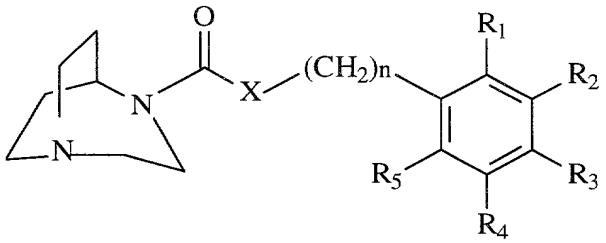
Version With Markings to Show Changes Made

In the Claims:

Claims 1 and 3 have been amended as follows:

1. (amended) A compound ~~Compound~~ corresponding to the general formula (I)



(I)

in which

X represents an oxygen atom or a group of formula NZ in which Z represents a hydrogen atom or a (C_1-C_6)alkyl group,

n represents a number 0, 1 or 2, and

R_1, R_2, R_3, R_4 and R_5 each represent, independently of each other, a hydrogen or halogen atom or a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenoxy or phenyl group optionally substituted with a halogen atom or a trifluoromethyl, cyano, hydroxyl, (C_1-C_6)alkyl or (C_1-C_6)alkoxy group, or alternatively R_2 and R_3 together form a group of formula $-OCH_2O-$ or $-CH_2CH_2CH_2CH_2-$, in the form of a base or of an addition salt with an acid.

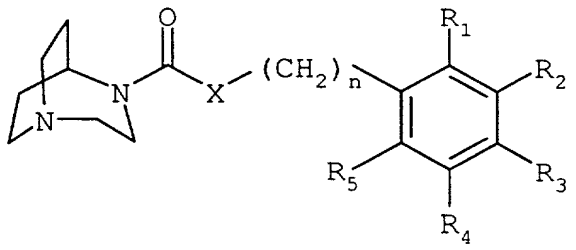
3. (amended) A pharmaceutical ~~Pharmaceutical~~ composition ~~, characterized in that it contains~~ comprising a compound according to Claim 1, combined with an excipient.

Claim 2 has been canceled.

Claims 4-6 have been added.

Derivatives of 1,4-diazabicyclo[3.2.2]nonane-4-carboxylates and -carboxamides, their preparation and their therapeutic application.

The subject of the present invention is compounds of general formula (I)



(I)

in which

X represents an oxygen atom or a group of formula NZ in which Z represents a hydrogen atom or a (C_1-C_6)alkyl group,

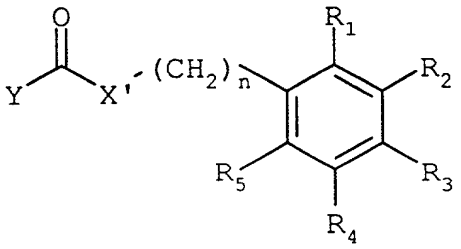
n represents a number 0, 1 or 2, and

R_1, R_2, R_3, R_4 and R_5 each represent, independently of each other, a hydrogen or halogen atom or a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenoxy or phenyl group optionally substituted with a halogen atom or a trifluoromethyl, cyano, hydroxyl, (C_1-C_6)alkyl or (C_1-C_6)alkoxy group, or alternatively R_2 and R_3 together form a group of formula $-OCH_2O-$ or $-CH_2CH_2CH_2CH_2-$.

The compounds of the invention may exist in the form of bases or of addition salts with acids.

To prepare the compounds of general formula

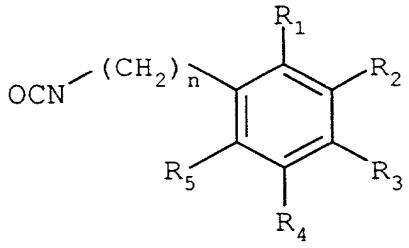
(I), 1,4-diazabicyclo[3.2.2]nonane may be reacted with a compound of general formula (II)



(II)

in which n, R_1, R_2, R_3, R_4 and R_5 are as defined above, X' represents an oxygen atom or a group of formula N-alkyl and Y represents a halogen atom, in the presence of a base such as triethylamine or pyridine.

To prepare the compounds of general formula (I) in which X represents an NH group, it is possible to react 1,4-diazabicyclo[3.2.2]nonane with an isocyanate of general formula (III)



(III)

in which n, R_1, R_2, R_3, R_4 and R_5 are as defined above, under conditions identical to those described above.

1,4-Diazabicyclo[3.2.2]nonane is described in *J. Med. Chem.* (1993) **36** 2311-2320.

The compounds of general formulae (II) and (III) are commercially available or may be prepared

according to any known methods.

The examples which follow illustrate the preparation of a few compounds of the invention. The elemental microanalyses, and the IR and NMR spectra confirm the structures of the compounds obtained. The numbers indicated in brackets in the titles of the examples correspond to those of the 1st column of the table given later.

In the names of the compounds, the hyphen "-" is part of the word, and the underscore "_" serves only for the break at the end of the line; it should be removed in the absence of a break, and should not be replaced either by a normal hyphen or by a space.

Example 1 (Compound No. 2).

4-Bromophenyl 1,4-diazabicyclo[3.2.2]nonane-4-carboxylate.

0.379 g (3.0 mmol) of 1,4-diazabicyclo[3.2.2]nonane and 0.84 ml (6.0 mmol) of triethylamine in 5 ml of dichloromethane are introduced into a 50-ml three-necked flask, the mixture is cooled to 0°C, 0.730 mg (3.1 mmol) of 4-bromophenyl chloroformate in solution in 3 ml of dichloromethane is added dropwise and the stirring is maintained at 0°C for 10 min.

The reaction medium is washed with water, the

aqueous phase is washed twice with dichloromethane, the combined organic phases are washed with a saturated aqueous sodium chloride solution, dried and the solvent is evaporated off under reduced pressure. The residue obtained is purified by silica gel chromatography, eluting with a 95/5/0.5 mixture of chloroform, methanol and aqueous ammonia. A crude product is obtained which is triturated in diisopropyl ether.

0.77 g of pure product is thus obtained in the form of a white solid.

Melting point : 115-116°C.

Example 2 (Compound No. 8)

N-Phenyl-1,4-diazabicyclo[3.2.2]nonane-4-carboxamide hydrobromide (1:1).

0.378 g (3.0 mmol) of 1,4-diazabicyclo[3.2.2]nonane in solution in 10 ml of acetonitrile is introduced into a 25-ml three-necked flask, a solution of 0.358 g (3.0 mmol) of isocyanatobenzene in 2 ml of acetonitrile is added at 3°C and the reaction medium is stirred for 10 min at room temperature.

The solvent is evaporated off under reduced pressure in order to obtain a solid which is dissolved in 30 ml of ethanol and which is treated with 0.53 ml of a 5.7 M hydrobromic acid solution in acetic acid at

50°C. The precipitate which forms is filtered and it is washed twice with ethanol.

0.649 g of product is thus obtained in the form of a white solid.

Melting point : 229-231°C.

Example 3 (Compound No. 10).

N-Methyl-*N*-phenyl-1,4-diazabicyclo[3.2.2]nonane-4-carboxamide hydrobromide (1:1).

0.69 ml (1.31 mmol) of a 20% solution of phosgene in toluene diluted by addition of 4 ml of toluene is introduced into a 25-ml three-necked flask (1.31 mmol) and the solution is cooled to 0°C. A solution of 0.127 g (1.12 mmol) of *N*-methylaniline and 0.11 ml of pyridine in 4 ml of toluene is added over 10 min and the mixture is kept magnetically stirred for 30 min at 0°C.

10 ml of ice-cold water are added and the organic phase is separated. In a 25-ml three-necked flask, this solution is poured over a suspension containing 0.15 g (1.12 mmol) of 1,4-diazabicyclo[3.2.2]nonane in 0.11 ml of pyridine and the mixture is stirred for 30 min.

10 ml of chloroform are added, the solution obtained is washed with 15 ml of a 1 M aqueous sodium hydroxide solution, the solvent is evaporated off and

the residue is purified by silica gel chromatography, eluting with a 95/5/0.5 mixture of chloroform, methanol and diethylamine.

0.31 g of product is obtained which is taken up in 5 ml of ethanol, 0.109 ml of an aqueous hydrobromic acid solution is added, the medium is diluted with addition of 5 ml of diisopropyl ether and the precipitate is recovered by filtration.

0.387 g of product is thus obtained in the form of a white solid.

Melting point : 292-293°C.

Example 4 (Compound No. 11).

[1,1'-Biphenyl-4-yl] 1,4-diazabicyclo[3.2.2]nonane-4-carboxylate hydrobromide (1:1).

4.1. [1,1'-Biphenyl-4-yl] chloroformate.

Preparation according to the method described in *Bull. Soc. Chim. Fr.* (1967).

2.00 g (11.75 mmol) of [1,1'-biphenyl]-4-ol in suspension in 50 ml of dichloromethane are introduced into a 50-ml three-necked flask, 0.47 g (11.75 mmol) of 60% sodium hydride in mineral oil is added portionwise, and the solvent is evaporated off under reduced pressure. A white solid is obtained which is added over 1 h to 6.84 ml (12.92 mmol) of a 20%

solution of phosgene in toluene at 30°C and left in contact for 3 h.

The solvent is evaporated off under reduced pressure, the residue is triturated in petroleum ether, filtered to remove the minerals and the solvent is evaporated off under reduced pressure.

0.89 g of crude product is thus obtained. Melting point : 36°C.

4.2. [1,1'-Biphenyl-4-yl] 1,4-diazabicyclo[3.2.2]nonane-4-carboxylate hydrobromide (1:1).

0.15 g (1.19 mmol) of 1,4-diazabicyclo[3.2.2]nonane and 0.33 ml (2.38 mmol) of triethylamine in solution in 10 ml of chloroform are introduced into a 50-ml three-necked flask, the mixture is cooled to 0°C and then the chloroformate previously obtained in solution in 10 ml of chloroform is added over 10 min. The mixture is stirred at 0°C for 10 min before allowing the temperature to rise to ambient temperature and it is left at room temperature for 18 h.

15 ml of 1 M sodium hydroxide are added and the mixture is extracted with chloroform. The solvent is evaporated off under reduced pressure and the residue obtained is purified by silica gel

chromatography, eluting with a 98/2/0.2 and then 96/4/0.4 mixture of chloroform, methanol and diethylamine.

0.31 g of product is obtained which is dissolved in 5 ml of ethanol, the solution is treated with 0.109 ml (0.96 mmol) of an aqueous hydrobromic acid solution, 5 ml of diisopropyl ether are added and the precipitate is filtered.

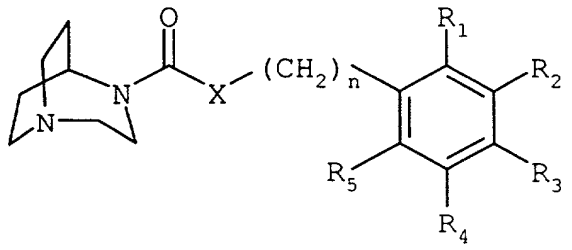
0.387 g of product is thus obtained in the form of a white solid.

Melting point : 292-293°C.

The table which follows illustrates the chemical structures and the physical properties of some compounds of the invention.

In the "Salt" column, "-" denotes a compound in the form of a base, "HBr" denotes a hydrobromide and "ox" denotes an oxalate, or ethanedioate; the acid:base molar ratio is indicated adjacent thereto.

Table



(I)

No.	X	n	R_1	R_2	R_3	R_4	R_5	Salt	m.p. (°C)
1	O	0	H	H	Cl	H	H	-	109-110
2	O	0	H	H	Br	H	H	-	115-116
3	O	0	H	H	CH_3	H	H	-	92-93
4	O	0	H	H	OCH_3	H	H	-	83.5
5	O	0	H	H	H	H	H	HBr 1:1	239-240
6	O	0	H	H	NO_2	H	H	-	98
7	O	0	H	H	F	H	H	-	66-68
8	NH	0	H	H	H	H	H	HBr 1:1	229-231
9	O	1	H	H	H	H	H	HBr 1:1	175.5-176
10	NCH_3	0	H	H	H	H	H	HBr 1:1	206-207
11	O	0	H	H	C_6H_5	H	H	HBr 1:1	292-293
12	O	0	Br	H	H	H	H	-	87-88
13	O	0	CH_3	H	H	H	H	ox 1:1	164-166
14	O	0	H	CH_3	H	H	H	ox 1:1	164-166
15	O	0	H	OCH_3	H	H	H	ox 1:1	152-154
16	O	0	H	CF_3	H	H	H	ox 1:1	95-96
17	O	0	H	OCH_2O		H	H	-	123-124
18	O	0	OCH_3	H	H	H	OCH_3	-	130-131
19	O	0	H	F	F	H	H	ox 1:1	171-173
20	O	0	H	Cl	Cl	H	H	ox 1:1	174-178
21	O	0	H	H	OCF_3	H	H	ox 1:1	204-205
22	O	0	H	$CH_2CH_2CH_2CH_2$		H	H	ox 1:1	202-203
23	O	0	H	H	OC_6H_5	H	H	-	107-108

The compounds of the invention were the subject of trials which demonstrated their therapeutic properties.

The compounds of the invention were also studied in relation to their affinity towards the nicotinic receptors containing the α7 subunit, according to the methods described by Marks and Collins, *J.Pharmacol.Exp.Ther.* (1982) **22** 554 and Marks et al., *Mol. Pharmacol.* (1986) **30** 427.

150- to 200-g male rats are decapitated, the whole brain is rapidly collected, homogenized with the aid of a Polytron™ grinder in 15 volumes of a 0.32 M sucrose solution, and then it is centrifuged at 1000 g for 10 min. The pellet is removed and the supernatant is centrifuged at 8000 g for 20 min at 4°C. The pellet is recovered and homogenized with the aid of a Polytron™ grinder in 15 volumes of double-distilled water at 4°C, and then it is centrifuged at 8000 g for 20 min. The pellet is removed and the supernatant and the buffy coat are centrifuged at 40,000 g for 20 min. The pellet is recovered, it is resuspended with 15 volumes of double-distilled water at 4°C and it is again centrifuged once at 40,000 g for 20 min before being stored at -80°C.

On the day of the experiment, the tissue is thawed slowly and it is suspended in 5 volumes of

buffer. 150 µl of this membrane suspension are preincubated at 37°C for 30 min, in the dark, in the presence or absence of the test compound. The membranes are then incubated for 60 min at 37°C, in the dark, in the presence of 50 µl of 1 nM [^{3}H]α-bungarotoxin in a final volume of 250 µl of 20 mM HEPES buffer containing 0.05% of polyethylenimine. The reaction is stopped by filtration on Whatman GF/C™ filters previously treated for 3 hours with 0.5% polyethylenimine. The filters are rinsed with twice 5 ml of buffer at 4°C, and the radioactivity retained on each filter is measured by liquid scintigraphy. The non-specific binding is determined in the presence of α-bungarotoxin at 1 µM final; the non-specific binding represents about 60% of the total binding recovered on the filter. For each concentration of compound studied, the percentage inhibition of the specific binding of [^{3}H]α-bungarotoxin is determined and then the IC_{50}, the concentration of compound which inhibits the specific binding by 50%, is calculated.

The IC_{50} values for the compounds of the invention which have the highest affinity are between 0.04 and 0.5 µM.

The results of the preceding trials show that the compounds of the invention are ligands for the α_7 subunits of the nicotinic receptor.

These results suggest the use of the compounds in the treatment or prevention of disorders linked to nicotinic receptor dysfunction, in particular at the level of the central nervous system or of the gastrointestinal system.

At the level of the central nervous system, these disorders comprise cognitive impairments, more particularly memory impairments, but also attention impairments, linked to Alzheimer's disease, to pathological ageing (Age Associated Memory Impairment, AAMI), to Parkinson's syndrome, to trisomy 21 (Down's syndrome), to Korsakoff's alcoholic syndrome, to vascular dementia (multi-infarct dementia, MID).

The compounds of the invention could also be useful in the treatment of the motor disorders observed in Parkinson's disease or other neurological diseases such as Huntington's chorea, Tourette's syndrome, tardive dyskinesia and hyperkinesia.

The compounds of the invention may also constitute a curative or symptomatic treatment of cerebrovascular accidents and of cerebral hypoxic episodes.

They may be used in the case of psychiatric pathologies : schizophrenia, depression, anxiety, panic attacks or obsessive-compulsive behaviour.

They can prevent the symptoms due to

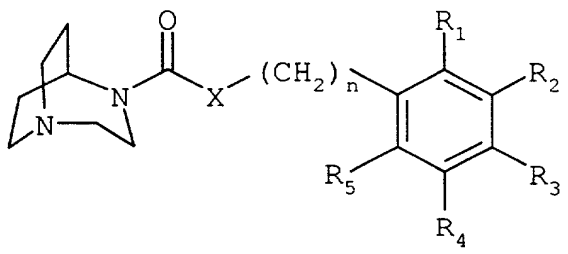
withdrawal from tobacco, from alcohol and from various substances which induce dependence, such as cocaine, LSD, cannabis, benzodiazepines.

At the level of the gastrointestinal system, the compounds of the invention could be useful in the treatment of Crohn's disease, ulcerative colitis, irritable bowel syndrome and obesity.

To this end, the compounds of the invention may be provided in any forms of compositions appropriate for enteral, parenteral or transdermal administration, such as tablets, sugar-coated tablets, hard gelatine capsules, soft gelatine capsules, oral or injectable suspensions or solutions such as syrups or ampoules, transdermal patches and the like, combined with suitable excipients, and containing doses to allow a daily administration of 0.01 to 20 mg/kg.

CLAIMS

1. Compound corresponding to the general formula (I)



(I)

in which

X represents an oxygen atom or a group of formula NZ in which Z represents a hydrogen atom or a (C_1-C_6)alkyl group,

n represents a number 0, 1 or 2, and

R_1, R_2, R_3, R_4 and R_5 each represent, independently of each other, a hydrogen or halogen atom or a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenoxy or phenyl group optionally substituted with a halogen atom or a trifluoromethyl, cyano, hydroxyl, (C_1-C_6)alkyl or (C_1-C_6)alkoxy group, or alternatively R_2 and R_3 together form a group of formula $-OCH_2O-$ or $-CH_2CH_2CH_2CH_2-$,

in the form of a base or of an addition salt with an acid.

2. Medicament, characterized in that it consists of a compound according to Claim 1.

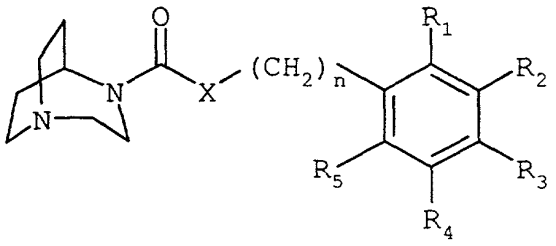
3. Pharmaceutical composition, characterized in that it contains a compound according to Claim 1, combined with an excipient.

DERIVATIVES OF 1,4-DIAZABICYCLO[3.2.2]NONANE-4-CARBOXYLATES AND -CARBOXAMIDES, THEIR PREPARATION AND THEIR THERAPEUTIC APPLICATION

SANOFI-SYNTHÉLABO

ABSTRACT

Compounds of general formula



(I)

in which X represents an oxygen atom or a group of formula NZ in which Z represents a hydrogen atom or an alkyl group, n represents a number 0, 1 or 2, and R_1, R_2, R_3, R_4 and R_5 each represent a hydrogen or halogen atom or a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, alkyl, alkoxy, phenoxy or phenyl group optionally substituted with a halogen atom or a trifluoromethyl, cyano, hydroxyl, alkyl or alkoxy group, or alternatively R_2 and R_3 together form a group of formula $-OCH_2O-$ or $-CH_2CH_2CH_2CH_2-$.

Application in therapy.

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

X Original _____ Supplemental _____ Substitute

As a below-named inventor, I hereby declare that:

My residence, citizenship and mailing address are given below under my name.

I/We believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

DERIVATIVES OF 1,4-DIAZABICYCLO[3.2.2]NONANE-4-CARBOXYLATES AND -CARBOXAMIDES, THEIR PREPARATION AND THEIR THERAPEUTIC APPLICATION

the application for which

___ is attached hereto.

___ was filed on _____ as United States
Application Serial No. _____
and was amended on _____ (if applicable)

X was filed on 21 March 2000 as PCT International
Application No. PCT/FR00/00697
and was amended on _____ (if applicable)

I/We have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above.

I/We acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in Section 1.56 of Title 37 of the Code of Federal Regulations, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I/We hereby claim foreign priority benefit under Section 119 (a) - (d) of Title 35 of the United States Code of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States identified below and also identify below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States filed by me on the same subject matter and having a filing date before that of the application(s) from which priority is claimed:

Country	Number	Filing Date	Priority Claimed Yes	Priority Claimed No
FR	9903934	30 March 1999	X	

I/We hereby claim benefit under Section 119(e) of Title 35 of the United States Code of any United States provisional application(s) identified below:

Application No.	Filing Date

I/We hereby claim benefit under Section 120 of Title 35 of the United States Code of any United States application(s) or PCT international application(s) designating the United States identified below:

Application Serial No.	Filing Date	Status

I/We hereby appoint Michael D. Alexander, Reg. No. 36,080; and Paul E. Dupont, Reg. No. 27,438, or any of them my/our attorneys or agents with full power of substitution and revocation to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith.

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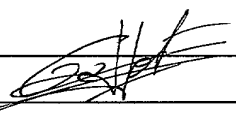
I/We hereby declare that all statements made herein and in the above-identified application of my/our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-50

Full name of first inventor GALLET Thierry

Inventor's signature  Date 19.07.01

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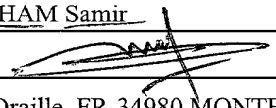
Inventor's signature  Date 30/07/2001

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